Title:

Cell migration by swimming: *Drosophila* adipocytes as a new *in vivo* model of adhesion-independent motility

Authors: Paul Martin[1], Will Wood[2] & Anna Franz[3,*]

Affiliations:
1 School of Biochemistry, Biomedical Sciences, University of Bristol, Bristol BS8 1TD, UK; School of Physiology, Pharmacology and Neuroscience, Biomedical Sciences, University of Bristol, BS8 1TD; School of Medicine, Cardiff University, Cardiff, CF14 4XN, UK
2 Centre for Inflammation Research, University of Edinburgh, Queen's Medical Research Institute, 47 Little France Crescent, Edinburgh, EH16 4TJ
3 Department of Cell and Developmental Biology, University College London, 21 University Street, London WC1E 6DE, UK and previously School of Biochemistry, Biomedical Sciences, University of Bristol, Bristol BS8 1TD, UK
* Corresponding author, email address: a.franz@ucl.ac.uk

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Abbreviations:

ECM: extracellular matrix

Abstract:

Several cell lineages migrate through the developing and adult tissues of our bodies utilising a variety of modes of motility to suit the different substrates and environments they encounter en route to their destinations. Here we describe a novel adhesion-independent mode of single cell locomotion utilised by *Drosophila* fat body cells – the equivalent of vertebrate adipocytes. Like

their human counterpart, these large cells were previously presumed to be immotile. However, in the *Drosophila* pupae fat body cells appear to be motile and migrate in a directed way towards wounds by peristaltic swimming through the hemolymph. The propulsive force is generated from a wave of cortical actomyosin that travels rearwards along the length of the cell. We discuss how this swimming mode of motility overcomes the physical constraints of microscopic objects moving in fluids, how fat body cells switch on other "motility machinery" to plug the wound on arrival, and whether other cell lineages in *Drosophila* and other organisms may, under certain circumstances, also adopt swimming as an effective mode of migration.

1. Introduction:

Cell motility is a fundamental cell behaviour that is crucial for a wide range of biological processes in health and disease. While many cells, particularly epithelial cells, tend to move as collective sheets, a number of cell lineages naturally migrate as individuals or small groups of cells. Germ cells migrate as single cells across the embryo on their long journey to contribute to forming the developing gonads. Immune cells also migrate individually often covering long distances to reach their various sites of action, such as a skin wound. Cell migration is also a key element of metastasis formation, when cancer cells, either as individuals or as small groups, gain the ability to detach from the primary tumor to invade distant sites.

Cell migration is an evolutionarily conserved series of mechanisms that has been heavily studied *in vitro* but also in a range of model organisms. *Drosophila melanogaster* has proven to be a particularly useful model organism to study several types of cell migration due to its sophisticated genetic toolset and *in vivo* live imaging potential. It has provided new valuable insights into the mechanisms behind collective cell migration e.g. through the study of border cells (collectively moving, heterogeneous groups of actively

and passively migratory cells, (reviewed in (*1*))), dorsal closure (collectively moving epithelial sheets which sweep toward one another to fuse in the embryonic midline, (reviewed in (*2*))) as well as single cell migration primarily through the study of germ cells (reviewed in (*3*)) and hemocytes (reviewed in (*4*)) which are the *Drosophila* innate immune cells. In this review we will focus on a recently discovered novel mode of "swimming" motility used by the pupal fat body cells of *Drosophila* to respond and migrate towards sites of tissue damage. We envisage that this newly described mode of motility may contribute to other *in vivo* cell migration strategies by lineages other than fat body cells/adipocytes.

2. Many different ways for a cell to move from A to B in tissues

Cell migration is not one single phenomenon. Depending on the cell type, developmental stage and environment through which the cell is moving, individual cells can migrate using several different modes of migration, and may even be able to switch between these modes. Mesenchymal cell migration is the best-studied mechanism by which a cell migrates and is classically studied in cells such as fibroblasts as they migrate over an extracellular matrix (ECM)-coated cover glass *ex vivo*, or on flat epithelial or basement membrane substrates *in vivo ((5), reviewed in (6, 7))*, as for example, when hemocytes developmentally disperse within the *Drosophila* embryo (reviewed in (*8*)). In cells using this migration mode, the polymerising actin network within lamellipodia pushes the membrane forward at the leading edge. At the same time strong integrin-based adhesions couple to contractile actin stress fibres, engaging the 'clutch' of the cell. This setup enables productive forward propulsion of the cell as new actin subunits are added to the front of anchored filament bundles. On highly adhesive surfaces, actomyosin contraction at the rear of the cell is required for detachment of its tail from the substrate. Many cell types, including hemocytes as they developmentally disperse or migrate to wounds in the *Drosophila* embryo (Fig.1A and B), are thought to employ this adhesion-dependent mesenchymal 'crawling' mode of cell migration.

By contrast, in the absence of integrin-dependent adhesion to the ECM cells are thought to use an amoeboid migration mode. The term ‘amoeboid’ has been used for a wide range of migration modes involving rather different types of leading-edge protrusions such as actin-rich pseudopods or actin-devoid blebs. Here we use ‘amoeboid’ to refer to cell migration characterised by a rounded cell shape, with little or no adhesion, fast speed and high levels of actomyosin contractility (reviewed in (*9*)). Blebbing is a well-studied type of amoeboid, adhesion-independent cell migration (reviewed in (*10*)). It is usually found in cells migrating within three-dimensional environments such as observed when zebrafish primordial germ cells migrate towards the embryonic genital ridges (reviewed in (*11*)). During blebbing, the contraction of the actomyosin network generates part-spherical membrane protrusions via hydrostatic pressure gradients. Myosin II-driven contraction causes tension in the actin network and a local rise in hydrostatic pressure. This can then either result in small ruptures in the cortical actin network or in the local detachment of the plasma membrane from the cortical cytoskeleton. The resulting cytosolic flow along the pressure gradient drives the protrusion of a membrane bleb. The maturing bleb then becomes lined by a new actin cortex and retracts in a myosin II-dependent manner to drive bleb retraction. Subsequently a new bleb forms. It appears that blebbing can drive motility even in the absence of focal adhesion-mediated substrate adhesions. Here, force-transmission is thought to be achieved by coupling the force generated through the rearward flow of cortical actin to the substrate through nonspecific friction, as shown for blebbing Walker carcinoma cells *ex vivo* (*12*).

3. But how about entirely adhesion-independent “swimming” as an *in vivo* cell migration strategy?

There are clear cut examples of how individual cells can migrate through fluids in the absence of contact with any substratum, and the best studied of these is the flagella-beating mode of migration used by swimming sperm.

3.1 The sperm of many animal species navigate their way to fertilise an egg by flagellar swimming

The sperm tail, is like a giant motile cilium (Fig.1C and D). It contains an axoneme which is generally composed of a central pair of microtubules surrounded by a circular arrangement of 9 doublet microtubules (Fig.1D) to which dynein motors are associated. These are able to contort the axoneme by being fixed to one doublet whilst “walking” up adjacent microtubule rods. A bend in the axoneme is powered by coordinated dynein “walking” on one side of the rod whilst those on the other side relax. As oscillatory waves of such “dynein walking” travel along the axoneme, they generate a sinusoidal wave beat that travels down the flagella to enable sperm swimming (reviewed in (*13*)). The fluid in which sperm swim dictates the physics of flagellar swimming and can vary from water through to thick cervical mucous depending on species. Evolution has consequently selected for a huge range of axoneme structures and flagellar lengths and oscillatory patterns to enable reliable fertilisation of the egg (reviewed in (*14*)). Similar to sperm, many protists and algae also use cilia or flagella to swim through liquids (reviewed in (*15*)).

3.2 Fat body cells in *Drosophila* pupae also appear to swim but without flagella

Sperm in vertebrates and in flies migrate by swimming within the female reproductive tract, a rather unusual environment. But is swimming used by any other cell type to migrate within the body itself? Our recent *in vivo* studies have shown that *Drosophila* pupal fat body cells also migrate by swimming in an adhesion-independent fashion but utilise an entirely different swimming mechanism to that exhibited by sperm (*16*).

Fat body cells are the *Drosophila* equivalent of vertebrate adipocytes and play many systemic roles through the development and adult life of the fly, including the regulation of metabolism (*17-20*), growth (*21-24*) and immunity

(reviewed in (*25, 26*)). The *Drosophila* pupa contains large numbers of giant polyploid, dissociated fat body cells that reside within the hemolymph, the fluid that fills the body cavity (Fig.1E). They derive from sheets of connected cells that dissociate from one another during the larval to pupal transition triggered by ecdysone signalling (*27, 28*). Like vertebrate adipocytes, fat body cells had previously been presumed to be immotile, but live imaging studies of their potential roles in response to tissue damage revealed that pupal fat body cells are not immotile, but actively migrate to wounds by swimming (*16*). Once at the wound site they fulfil several key local functions including clearing the wound of cell debris, sealing the epithelial wound gap and locally releasing antimicrobial peptides to control wound infection (*16*).

4. How do fat body cells swim?

Fat body cells actively migrate to wounds using a novel, actomyosin-driven, peristaltic mode of swimming motility. Most cells in tissue culture or *in vivo* within tissues, such as *Drosophila* hemocytes appear to migrate by adhering to and crawling over a substratum using lamellipodia (Fig.1A and B and Fig.2A and B). In contrast, migrating fat body cells do not seem to need to adhere to any surface; indeed, often they do not contact another cell or ECM en route to the wound (Fig.2A). As fat body cells “swim” towards the wound, they mostly display a rounded cell shape without any indication of protrusions at the front of the cell such as lamellipodia, filopodia or blebs (Fig.2A, C and D). Instead, they undergo actin-based peristaltic waves of contraction whereby cortical actin periodically disappears from the front of the cell and moves to its rear, thus propelling the cell in the opposite direction ((*16*), Fig.2A and D). It could be argued that this disappearance of actin from the front of the fat body cell is somewhat analogous to the formation of a giant front-end bleb, and certainly the underpinning molecular mechanisms might be related. Indeed, the resulting peristaltic cellular movement is also dependent on myosin activity. These movements are constantly occurring within fat body cells in unwounded pupae, but in an undirected fashion; however, upon wounding the waves become strongly directed allowing these cells to rapidly

migrate to wounds with highly increased directional persistence but an unchanged speed of around 3.5μm/min. This speed is not dissimilar to the speed of migrating hemocytes (2.6μm/min, (*29*)).

Targeted migrations of this type beg the question as to what might be the specific attractant(s) that draw the cell to its destination? While it is clear that immune cells are drawn to wounds by a complex mix of early damage signals (danger-associated molecular patterns) including Hydrogen peroxide (*30-32*) and ATP (*33*), and later chemokine attractants (reviewed in (*34*)) we still do not know whether these signals might attract fat body cells too, or whether an entirely different set of attractants are driving their recruitment to sites of damage.

5. Do other cells use similar migration modes as part of their motility portfolio?

Adhesion-independent migration, as used by fat body cells, has recently emerged as an alternative migration mode that has been described for several other types of cells including amoeba, lymphocytes and some cancer cells ((*35*), reviewed in (*9, 12, 36*)). Cells encountering a more open 3D environment offering few or no adhesive attachment points are thought to favour this mode of migration (reviewed in (*37*)).

6. What drives force-generation in fat body cells?

As described previously, force-generation in mesenchymal migration is driven by actin-polymerisation in lamellipodia at the cell's leading edge in combination with myosin-based contraction at the rear to disassemble adhesion sites. In contrast to this, propulsive forces in cells migrating in an adhesion-independent manner tend to be generated by retrograde flows of the actomyosin cortex combined with contraction at the rear ((*38-41*), reviewed in (*12*)). This clearly shares parallels with the rearward peristaltic

actin waves observed in fat body cells, suggesting that this could also be the mechanism of force generation in these cells.

7. How are the internal forces generated through retrograde flow of cortical actin transduced to the environment to drive fat body cell motility?

7.1 Four different models of force generation in adhesion-independent cell migration

Cells migrating by adhesion-dependent lamellipodia-driven migration apply rearward forces against extracellular media to propel themselves forward. It is unclear how this force-transduction is achieved in adhesion-independent migration in the absence of such adhesions. Four models have been proposed: force-transmission driven by “chimneying” between two opposing substrate faces, the intercalation of lateral cell protrusions with gaps in the substrate, non-specific friction between cell and substrate, and swimming by noncyclic cell shape deformations (reviewed in (*9*)). Only the last of these is entirely independent of any interactions with (or the close proximity to) a solid substrate. Hence, it best describes the migration of fat body cells through hemolymph to wounds, since these cells are not seen to be interacting with any substrate or other cells as they migrate. Similar to fat body cells, several other cell types have been reported to migrate by swimming: Amoebae and neutrophils have been shown to swim when in viscous *in vitro* solutions (*42*). Moreover, a study in macrophages which utilised optogenetic techniques to activate Rho at the cell rear showed how this induced macrophage motility even when cells were suspended in liquid (*35*).

7.2. Force-transduction to the environment in swimming fat body cells

It still remains unclear how the intracellular force generated by retrograde waves of cortical actin might be transduced to the extracellular environment in

the absence of adhesion to drive the forward movement of swimming fat body cells. It has previously been presumed that while swimming works for large multicellular organisms, it cannot operate at the microscopic cell level, where viscous forces are many orders of magnitude higher than inertial forces (i.e. at low Reynolds number (*43*)) and hence geometrically reciprocal cell shape changes should not generate propulsive forces (reviewed in (*9*)). However, recently this view has been challenged and shown to only be true for simple Newtonian fluids, like water (*44*). Moreover, swimming in a non-Newtonian fluid (a viscous fluid containing particles such as the hemolymph through which fat body cells move) is thought to be possible if the cell shape changes of migrating cells are nonreciprocal (reviewed in (*9*)), which might be true for fat body cells migrating to wounds. It might be expected that an extending protrusion such as a bleb would push a cell forward but the subsequent retraction would move the cell backwards again resulting in no net movement. However, a mathematical model study has recently shown that net cell displacement can occur even in a low Reynolds number environment in large part because the shape change of the cell during bleb expansion and bleb retraction are not the same (*45*).

It is also possible that fat body cells make use of other mechanisms for force-transduction such as rearward surface treadmilling. Two mathematical studies have suggested surface treadmilling without cell shape changes as a mode of locomotion for microswimmers at low Reynolds number (*46, 47*). They predicted that if a cell's surface flows in one direction at a constant speed, viscous forces generated tangential to the cell surface can propel the cell through fluid in the opposite direction at almost the same speed. Indeed, swimming by surface treadmilling is thought to be remarkably more efficient than the rotating helical flagellum of bacteria and locomotion by virtue of shape strokes (*47-50*). This ‘‘surface treadmilling’’ mechanism has been proposed to contribute to the migration of several cell types ((*42*), reviewed in (*51*)), including the swimming macrophages described earlier (*35*). In this study the authors demonstrated how actomyosin contractility at the cell rear leads to a flow of the actin cortex which is coupled to the plasma membrane, which, in turn, generates retrograde membrane flow to drive cell migration by

generating rearward forces against the viscous fluid (*35*). Importantly, this study supports the prediction that tangential forces are sufficient to propel a cell forward in the absence of any adhesive forces.

Whether the rearward actin flow observed in fat body cells is also coupled to surface membrane flow and/or cell shape changes remains to be investigated and will enable a deeper understanding of the mechanism that drives migration of these large cells. Importantly, fat body cells represent the first *in vivo* model to study adhesion-independent migration by swimming using high-resolution live imaging. Future studies of fat body cell migration in *Drosophila* open up genetic opportunities to further our understanding of how other cell types may migrate in similar ways when they are required to move through viscous fluid or within a loose connective tissue in an adhesion-independent manner (i.e. to swim), rather than to crawl over a substratum.

8. Might fat body cells have other migration modes besides peristaltic swimming?

It is entirely possible that fat body cells can also make use of other mechanisms to move towards a target. Our observations of swimming fat body cells were made in the pupal ventral thorax where there is a rather low density of fat body cells in the hemolymph; however, in other regions of the pupae fat body cells are more densely packed analogous to people in a crowded swimming pool, and here we do see random contacts between fat body cells as well as between fat body cells and other cell types such as hemocytes and the underside of epithelial sheets. In such regions, these contacts might occasionally allow for the actomyosin-generated internal forces to be coupled to the substrate via friction just as observed in non-adherent Walker cells migrating in a confined microfluidics channel (*12*), and this may act as an addition to their purely swimming motility.

While it is commonly believed that migrating cells generally favour certain migration modes, it has recently become clear that many cell types such as

disseminating cancer cells are capable of switching between migration modes. This may allow them to select the most efficient migration mode for a given environment as they migrate through complex and changing tissue landscapes. Interestingly, fat body cells also appear to be able to interconvert their mode of motility, to a degree, as their environment changes. They swim through the hemolymph towards the site of tissue damage, as described above. However, once they reach the epithelial wound site, and first make contact with healthy wound epithelial margin cells they begin to extend actin-rich lamellipodia from their apical surfaces (*16*). These structures are reminiscent of the lamellipodia used by hemocytes to migrate and show the same localisation of the actin regulatory proteins Fascin and Fimbrin. However, rather than driving any further significant cell translocation, these dynamic lamellipodia appear to be used by fat body cells to explore the wound area and to anchor the cell at the wound site by concentrating lamellipodia in a ring formation around the closing wound margin to create a tight seal (Fig.2E-H). If the wound gap is large then several fat body cells and their extending lamellipodia will cooperate to seal the wound.

Interestingly, extensive dynamic blebs can often been seen on the apical surface of fat body cells once these cells have arrived in the vicinity of the wound (Fig. 2I and J). This blebbing might help the cell to shuffle somewhat to wedge itself more firmly into the wound hole in order to form an effective plug.

This suggests that, like other cell types, fat body cells are capable of switching their mode of protrusion formation ‘on the go’, as the cells face changes in their environment. Rather strikingly, fat body cells can even form two different protrusion types, blebs and lamellipodia, simultaneously at the wound site, whereas most cells which use these protrusions for motility build either one or the other.

9. Conclusions and unanswered questions:

Individual cells are tasked with migrating through a variety of environments and as we highlight in this review, one such environment is within a fluid, and at least one cell type *in vivo* appears to do this by a newly described mode of "peristaltic" swimming. We suspect that other cells *in vivo* can and do adopt this strategy on occasions and when the environment demands. It will be interesting to investigate how broadly this mode of motility is used and how it is switched on and off in a migrating cell. Fat body cells in *Drosophila* will provide a powerful tool for investigating this further since they are amenable to live imaging, in part because of their large size, they can easily be genetically manipulated, and because in some scenarios, at least, they appear to specialise in this mode of motility.

9.1 Are adipocytes motile in other animals?

The observation that fat body cells are motile cells, which actively migrate to wounds is unexpected and has not previously been observed for adipocytes in any other organism. However, our findings raise the interesting question as to whether vertebrate adipocytes might also have the capacity to migrate. In that regard, previous mammalian wound studies have found that adipocytes repopulate murine wounds, and suggested that some may have migrated from distant sites (*52*). Moreover, two more recent studies have indicated that adipocyte migration might contribute to myocardial fat deposition during heart regeneration (*53*) and to adipocyte accumulation in the inflamed skin of a murine model of induced atopic dermatitis (*54*). It will be fascinating to discover whether some sub-populations of vertebrate adipocytes are indeed motile and whether they utilise similar migratory strategies to those highlighted in *Drosophila* fat body cells.

9.2 How universal might it be for cells to switch from adhesion-dependent to "swimming" modes of motility?

It is now well accepted that cells, particularly cancer cells, have the capacity to switch between mesenchymal and amoeboid modes of motility (reviewed in

(*55*)), and so we wonder whether it might also be the case that other cells might also include peristaltic swimming in their portfolio of cell motility mechanisms. Immune cells and cancer cells both occasionally inhabit fluid filled spaces including blood and lymphatic vessels and the peritoneal cavity. It has previously been presumed that cell movement in these situations, for example as ovarian cancer cells disperse within the abdomen, is entirely dependent on passive flow, but potentially these are occasions when cells may actively swim.

Figure legends:

Fig. 1:

(A) Confocal microscopy image of two hemocytes (labelled with GFP-lifeact, shown in yellow) migrating underneath the epithelium (labelled with Ubq-RFP-tubulin, shown in red) in the *Drosophila* pupal wing.

(B) Schematic showing the dispersal of hemocytes along the ventral midline during embryonic development in *Drosophila*. Hemocytes initially migrate from the anterior and posterior ends of the embryo in two lines towards each other to populate the entire ventral midline (arrows depict direction of migration). Once they meet, they migrate laterally, eventually forming three lines that span the developing ventral nerve cord (central nervous system equivalent).

(C) Image of the fertilisation of a sea urchin egg by swimming sperm.

(D) Schematic of a swimming sperm cell (pink) showing the head, middle piece and flagellum. An emission electron microscopy image (inset) of the axoneme of a *Drosophila* sperm cell is shown in cross section revealing the typical ‘9+2’ microtubule arrangement.

(E) An image of a fat body cell in the thorax of a *Drosophila* pupa (stained with methylene blue) containing large lipid droplets (white).

(F) Schematic of a fat body cell (green) migrating to an epithelial wound (pink) by swimming through the hemolymph (purple). Arrows depict direction of migration.

Scale bars: 20μm (A, E)

Fig. 2:

(A) Schematic of a fat body cell (green) migrating to an epithelial wound (pink) by swimming through the hemolymph (purple). This involves rearward flow of cortical actin (white). A hemocyte (purple) also migrates to the wound, but moves along the epithelium by mesenchymal cell migration using actin-rich lamellipodia at the cell front. Once at the wound, the fat body cell plugs the wound gap by lamellipodia-driven cell anchoring and releases antimicrobial peptides to fight infection. Moreover, the fat body cell, together with the hemocyte, clears cellular debris off the wound site by phagocytosis.

(B) Confocal microscopy image showing the lamellipodia within a hemocyte (labelled with Cherry-Fascin in red and GFP-Ena in green) migrating underneath the epithelium in the *Drosophila* embryo.

(C) Confocal microscopy image of a fat body cell (labelled with Lpp-Gal4+UAS-GFP in green) that plugs the wound gap having migrated to an epithelial wound (outlined with arrowheads) in the pupal thorax. The nuclei of the epithelium are labelled with Histone-RFP (red).

(D) Timelapse series of a wave of cortical actin (labelled with GMA (GFP-tagged actin-binding domain of moesin), shown in green) traveling rearwards in a fat body cell as it migrates to a wound (arrow depicts direction of migration).

(E-H) Schematics (E, G) and confocal microscopy images (F, H) depicting the lamellipodia (arrows, labelled with GFP-Fascin in green in F and with Cherry-Fimbrin+GFP-Ena in red and green in H) on the apical side of a wound-associated fat body cell (wound outlined with arrowheads in F). E and F show lateral views, and G and H show en face views.

(I-J) Schematic (I, lateral view) and confocal microscopy image (J, en face view) depicting blebs (arrows, labelled with cytosolic GFP) on the apical side of a wound-associated fat body cell.

Scale bar: 20μm (D)

Supplementary movie legend:

Movie S1: An actomyosin wave propels the fat body cell towards a wound (related to Fig. 2D)

Timelapse of a wave of cortical actin (labelled with GMA (GFP-tagged actin-binding domain of moesin), shown in green) traveling rearwards in a fat body cell as it migrates to a wound.

Scale bar: 20μm

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